Amendments to the Specification

Please amend the section entitled CROSS REFERENCE TO RELATED APPLICATIONS on page 1, lines 6-8 as follows:

This application is a continuation of U.S. patent application USSN 09/909,684, filed July 20, 2001 and claims the benefit of U.S. Provisional Application serial number 60/277,531 filed March 21, 2001 and 60/225,695 filed August 16, 2000.

Please replace the paragraphs identified below with the following:

Page 1, lines 12-18:

The present invention relates to a novel process for the preparation of (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes by stereoselective reduction of the corresponding oxo compounds. The substituted butanes produced in accordance with the process of the inventions are precursors of hydroxyethylamine isostere sub-units present in many molecules therapeutically useful as inhibitors of angiotensin converting enzyme, renin and HIV-protease.

Page 3, lines 20-24:

The present invention is directed to a novel stereoselective process for the preparation of (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes by the reduction of the corresponding keto group containing compounds by certain species of *Rhodococcus* and *Brevibacterium.* The products are obtained in high yield and in excellent diastereomeric purity.

Page 4, lines 3-5:

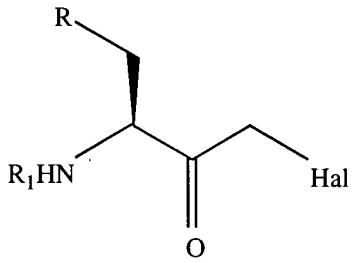
The process of the present invention provides an advantageous synthesis for the (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes represented by the formula

Page 4, lines 13-27

The substituted butanes represented by formula I are useful as intermediates in the synthesis of molecules that are inhibitors of ACE, renin and HIV proteases. The activity of such molecules against HIV proteases makes them very valuable in the treatment of retroviral infections such as AIDS. Such compounds and their use are disclosed, for example, in U.S. Patent No. 5,849,911, the disclosure of which is incorporated herein by reference. A particularly important AIDS compound disclosed in U.S. Patent No. 5,849,911 is [3S-(3R*,8R*,9R*,12R*)]-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6{[4-(2-pyridinyl)phenyl]methyl}-2,3,6,10,13-pentaazaretetradecanedioic acid dimethyl ester. This compound may be directly synthesized from the (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes represented by formula I. The fact that the process of the present invention produces a very high yield of the trans (1S,2R) [1S,2S] enantiomer of the substituted butanes represented by formula I makes it very important to the ultimate efficiency of the synthesis of the therapeutic compound described above.

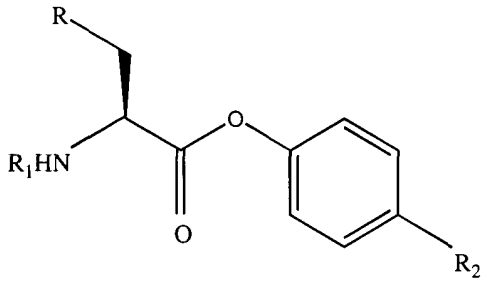
Page 6, line 11- Page 7, line 14:

The starting materials for the process of subject process for preparing the (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes represented by formula I are the corresponding keto group-containing compounds represented by the formula

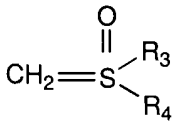


II

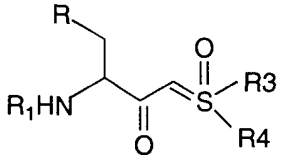
wherein Hal, R and R_1 are as defined above. The compounds represented by formula II can be prepared by techniques described in the literature and known to those of ordinary skill in the art. A preferred process for forming the compounds represented by formula II is disclosed in co-pending patent application U.S. Serial No. 09/908,516, filed July 18, 2001 [Docket GY55], the disclosure of which is incorporated herein by reference. In this method, an aryl ester represented by the formula



wherein R and R_1 are as defined above and R_2 is hydrogen or nitro and may be substituted in the ortho or para position on the phenyl ring is reacted with a sulfur ylide, i.e. a compound containing a function represented by the formula



to produce an intermediate keto ylide compound represented by the formula



wherein R and R_1 are as defined above and R_3 and R_4 are selected from the group consisting of alkyl, substituted alkyl and aryl. The keto ylide compound represented by

the above formula is then converted to the keto group-containing compounds represented by formula II by reaction with a source of chloride, preferably a basic source of chloride, most preferably lithium chloride, and an organic acid, for example, methanesulfonic acid.

Page 7, line 16 - Page 17, line 8:

The (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes represented by formula I above are important intermediates of in the synthesis of molecules that are inhibitors of ACE, renin and HIV proteases. The activity of such molecules against HIV proteases makes them very valuable in the treatment of retroviral infections such as AIDS. Specifically, the (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes represented by formula I are treated with a suitable base to convert them to the corresponding epoxides represented by the formula shown below

Page 8, line 14 - Page 9, line 6:

The stereoselective reduction of the (1S)-1-halo-2-oxo-3-(protected)amino-4-substituted butanes represented by formula II above to form the (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes represented by formula I is carried out in accordance with the present invention by reaction with an oxidoreductase enzyme, or preferably, a microorganism that supplies an oxidoreductase enzyme capable of catalyzing the enzymatic reduction of the ketones represented by formula II. The cells of the microorganism may be in the form of intact wet cells or dried cells such as lyophilized, spray-dried or heat-dried cells, or in the form of treated cell material such as ruptured cell or cell extracts. While a large and varied number of microorganisms are known to supply some form of oxidoreductase, it has been found in accordance with the present invention that only selected species of Rhodococcus and *Brevibacterium* catalyze the reduction of the compound represented by formula II to form the desired (1S,2R) [1S,2S]-1-halo-2-hydroxy-3-(protected)amino-4-substituted butanes in high quantitative and enantiomeric yield. These species are *Rhodococcus erythropolis* ATCC 4277, *Rhodococcus erythropolis* DSM 6971 and *Rhodococcus sp.* ATCC 21227, *Rhodococcus*

erythropolis ATCC 27854 *and Brevibacterium sp.* ATCC19653. The term "ATCC" as used herein refers to the accession number of the depository for the particular organism, i.e. the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852. The term "DSM" refers to the German Collection of Microorganisms and Cell Cultures, Branschweig, Germany.

Page 13, line 24 - Page 14, line 5:

Rhodococcus erythropolis ATCC 4277 cells (1 mL) was inoculated into 100 mL of Medium 1 as noted above in a 500 mL flask and incubated at 28°C and 200 RPM on a shaker for 22 hours. The pH of 50 cells broth was adjusted to pH 7.0 with 1 M potassium phosphate buffer. Glucose was added to the cell broth at 25 mg/mL and 50 mg. of (1S)-[N-(1-benzyl-2-oxo-3-chloro)propyl]carbamic acid t-butyl ester (the substrate) was added thereto. The biotransformations (reductions) were carried out at 28°C and 200 RPM on a shaker. At predetermined times the reaction mixtures were quenched with two volumes of a 60:40 mixture of t-butyl methyl ether and toluene, and the separated organic phase was filtered through a 0.2 micron filter and collected. Two mL of the organic phase was evaporated to dryness under a stream of nitrogen and the residue taken up with 1 mL of acetonitrile, filtered and analyzed by HPLC for (1S,2R) [1S,2S]-[N-(1-benzyl-2-hydroxy-3-chloro)propyl]carbamic acid t-butyl ester (the product). The results are summarized in Table 1 below.

Page 14, line 12 - Page 15, line 4:

The substrate and the product for this Example were as described in Example 1. Cells of *Rhodococcus erythropolis* ATCC 4277 and *Rhodococcus erythropolis* DSM 6971 (1 mL) were individually inoculated into 100 mL portions of Medium 1 as noted above in a 500 mL flask and incubated at 25°C and 280 RPM on a shaker for 48 hours. One hundred mL of each culture was innoculated into 15mL of Medium 1 combined in a fermentor. Growth in the fermentor was carried out at 25°C, 15 LPM (liters per minute) aeration and 500 RPM agitation for 36 hours. Cells were harvested from the fermentor and used for the enzymatic conversion (biotransformation) of (1S)- [N-(1-benzyl-2-oxo-

3-chloro)propyl]carbamic acid t-butyl ester (the substrate) to (1S,2R) [1S,2S]-[N-(1-benzyl-2-hydroxy-3-chloro)propyl]carbamic acid t-butyl ester (the product). Cell suspensions were prepared by suspending the cells, 20 grams in 100 mL of 64 mM potassium phosphate buffer, pH 7.0. To each suspension was added 25 mg/mL of glucose and a predetermined concentration of substrate. The biotransformation of the substrate to the product was carried out at 28°C and 160 RPM on a shaker. At predetermined times the reaction mixtures were quenched and the product obtained and analyzed as described in Example 1. The results are summarized in Table 2 below.

Page 23, lines 3-10:

The present invention relates to a process for the stereoselective enzymatic reduction of 1-halo-2-oxo-3-(protected)amino-4-substituted-butanes utilizing certain species of *Rhodococcus* and *Brevibacterium*. The product 1-halo-2-hydroxy-3-(protected)amino-4-substituted-butanes, which are useful as intermediates in the synthesis of compounds that are inhibitors of ACE, renin and HIV proteases, are obtained in high yield and, particularly, in very high diastereomeric purity. The process is advantageously highly selective for the (1S,2R) [1S,2S] enantiomer of the product.